Predictors of Long-term Anxiety and Depression in Uveal Melanoma Survivors: A Cross-lagged Five-year Analysis

Stephen L. Brown,[1] Peter L. Fisher,[1,2] Laura Hope-Stone[1,2,3] Rumana N. Hussain,[3] Heinrich Heimann,[3]Bertil Damato[3] & M. Gemma Cherry,[1,2]

1. Department of Psychological Sciences, University of Liverpool.
2. Clinical Health Psychology Service, Linda McCartney Centre, Royal Liverpool and Broadgreen University Hospital NHS Trust.
3. Liverpool Ocular Oncology Centre, Royal Liverpool and Broadgreen University Hospital NHS Trust.

Keywords: Cancer; Anxiety; Depression; Uveal Melanoma; Cross-Lagged Analysis; Psycho-oncology.

Correspondence: Stephen Brown, University of Liverpool, Liverpool L69 3BX,UK. E: slbrown@liverpool.ac.uk

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pon.5514

Abstract

Objective: Cancer survivors commonly experience long-term anxiety and depression. Anxiety and depression might result from problems emerging during survivorship rather than illness and treatment. This study tested three potential causal paths: 1) concerns about physical symptoms and functional problems and fear of cancer recurrence (FCR) arising during survivorship *directly* cause anxiety and depression, 2) an *indirect* path whereby FCR mediates effects of concerns about physical symptoms and functional problems on anxiety and depression, and 3) a *reciprocal* path whereby anxiety and depression cause concerns about physical symptoms and functional problems and FCR, which exacerbate later anxiety and depression. **Methods**: Sample of 453 uveal melanoma survivors who completed observations 6-, 12-, 24-, 36-, 48- and 60-months post-diagnosis and did not miss two consecutive observations. Cross-lagged analyses were conducted to predict Hospital Anxiety and Depression Scale subscale scores. Symptoms and functional problems were measured using the EORTC OPT 30 scale, and FCR operationalised by the EORTC OPT 30 worry about recurrence scale. Covariates were age, gender, treatment modality and visual acuity of the fellow eye and chromosome-3 status (which accurately predicts 10-year survival), worry and anxiety or depression. **Results**: All paths received some support, although the indirect path emerged only for anxiety in females. Concerns about physical symptoms, functional problems and FCR originated in survivorship and appeared to both influence and be influenced by anxiety and depression. **Conclusions**: Findings emphasise the importance of actively monitoring survivors to prevent, detect and intervene in the development of anxiety and depression during survivorship.

Background

Between 15 and 26% of cancer survivors experience anxiety or depression two to five years after treatment,[1-4] with anxiety and depression defined by structured interviews or clinically significant scores on measures of symptomatology. In addition to reducing quality of life,[5] anxiety and depression reduce treatment engagement,[6] medical recovery, satisfaction with health services[7] and adjustment to life post-treatment.[1,8]

Research typically involves prospectively predicting anxiety and depression from theoretically-derived variables, measured at baselines established at initial diagnosis or cessation of primary medical treatment. Beyond temperamental variables, such as neuroticism, this research has produced little evidence that demographic, psychological, social or clinical factors reliably predict longer-term distress in cancer survivors.[9] Cross-lagged studies in the mental health literature show that recent events, such as life experiences, predict anxiety and depression.[10] Survivor studies rarely examine whether events occurring after treatment predict later anxiety and depression symptoms. Thus, events occurring during survivorship, such as worsening physical symptoms or functional problems, is overlooked.[9] This paper examines these impacts in a prospective study of Uveal Melanoma (UM) survivors

Concerns about Physical Symptoms, Functional Problems and Fear of Cancer Recurrence

Survivors commonly experience physical symptoms that cause pain, discomfort, inconvenience or disfigurement. Further, physical symptoms can degrade functioning in routine life tasks.[11] Concerns about physical symptoms and functional problems frequently emerge during cancer survivorship or persist long into it.[12] Physical symptoms and functional problems increase vulnerability to anxiety and depression in multiple chronic illness populations,[13] and are cross-sectionally associated with anxiety and depression in survivors.[2,4,12,14] Further, many survivors are at risk of local and metastatic cancer recurrence. A large literature on the aetiology and effects of survivors' fear of cancer recurrence (FCR) has

recently emerged.[12,14] Both objective risk and FCR are cross-sectionally associated with anxiety.[12,14]

Studies cited above suggest that physical symptoms, functional problems and FCR might cause anxiety and depression, but their cross-sectional designs provide weak evidence of causality. Understanding causal pathways is important for intervention development. In this study, we prospectively tested three feasible paths, each suggesting different prevention and treatment interventions.

The first path is *direct*, whereby the strain of physical symptoms, functional problems **and FCR** cause anxiety and depression.[2,4] The second path is *indirect*. Somatic phenomena, such as symptoms and functional problems, cause survivors to subjectively appraise their causes and implications.[15] Symptoms that are similar to survivors' initial cancer symptoms may be interpreted as recurrences, or simply activate traumatic memories of illness and treatment.[16] These appraisals may lead to FCR.[15] Thus, FCR might mediate relationships between physical symptoms, functional problems and anxiety and depression. One prospective study shows evidence of mediation.[17] However, this study was conducted over two years and cannot address longer-term outcomes experienced by survivors.[2,4]

Third, paths may be *reciprocal* - survivors might experience downward spirals, whereby anxiety or depression cause deteriorations in actual or perceived physical symptoms, functional problems or FCR. This deterioration could aggravate the initial anxiety or depression. Anxiety and depression might increase concerns about physical symptoms or functional problems in three ways. They can cause biological changes (e.g., immune response changes),[18] behavioural changes (e.g., reducing disease-modifying behaviours such as medication adherence),[19] or simply amplify concerns about existing disease.[20]

In this study, the three paths hypothesised above are examined in a population of patients with UM.

Uveal Melanoma

UM mostly originates (90%) from the choroid of the eye and is generally treated by surgery or radiotherapy.[21] UM is uniquely suited to investigations into problems of survivorship. First, physical symptoms and functional problems are mainly confined to survivorship. Pre-treatment symptoms, such as visual disturbances, can occur but are unlikely to be debilitating.[22] Surgical and radiotherapy treatments can be experienced as difficult, but chemotherapy is rare. Thus, to survivors, post-treatment symptoms are often novel and unexpected, and the psychological effects consequently may be stronger. Further, iatrogenic problems (ocular irritation, visual disturbances and pain) frequently emerge several years after treatment.[23,24]

Second, FCR is based in subjective appraisals that may not reflect objective vulnerability. In interpreting paths related to FCR, it is important to understand the extent to which FCR is objectively grounded. If FCR is independent of vulnerability,[14] interventions should aim to address patients' tendencies toward worry and any misperceived vulnerability.[15] However, if worry derives from objective vulnerability, the therapeutic goal becomes helping high-risk individuals to tolerate it.[25] Studies note the invariance of FCR between groups with different objective risk profiles,[14, 26] but relationships between worry and objective risk cannot be directly examined between individuals because objective recurrence risks are difficult to estimate.[14] A UM population allows us to overcome this problem. Unlike other cancers, UM recurrence risk can be predicted with sufficient accuracy to provide survivors with reliable life expectancy estimates.[22] 40-50% of survivors will develop metastatic disease within 10 years, for which treatment rarely prolongs life. This risk can be measured and life expectancy estimated.[22] Patients in our sample were offered prognostic testing and informed of prognoses. Statistical control of prognoses exposes worry of metastatic death that is based on inaccurately high risk perceptions.

Study Objectives

Our aim was to prospectively examine pathways between physical symptoms and functional problems, FCR and anxiety and depression in UM survivors. We used a cross-lagged, five-year, six-observation design to examine potential paths. The objective was to test

three paths: 1) *direct* paths - concerns about physical symptoms, functional problems and FCR uniquely predict anxiety and depression at the next observation; 2) *indirect* paths - physical symptoms and functional problems predict FCR at the next observation, which in turn predicts later anxiety and depression; and 3) *reciprocal* paths - anxiety and depression predict physical symptoms, functional problems and FCR, which predict anxiety and depression at the next observation.

Methods

Participants and Procedure

The study was approved by the Health Research Authority NorthWest – Liverpool Central Ethics Committee (03/06/072/A) in accordance with the Declaration of Helsinki 2006. The sampling frame was a consecutive series of adult patients from England or Wales treated for posterior UM (i.e., choroid and ciliary body) between April 1st 2008 and December 31st 2014 at the Liverpool Ocular Oncology Centre (LOOC), one of the largest tertiary referral centres in the United Kingdom. Cross-lagged designs typically show small effect sizes due to autoregressive effects. A priori power analysis showed a sample size of 476 necessary to detect a very small effect size of .02 (alpha=.05, power=.080). Diagnosis and treatment of UM was based on clinical and tumour characteristics described by Damato and Heimann.[27] Most patients had ruthenium plaque radiotherapy or proton beam radiotherapy. If the tumour was unsuitable for radiotherapy, because of its location or size, patients underwent trans-scleral local resection, trans-retinal endoresection or enucleation (i.e., amputation) of the affected eye. Patients were also offered prognostic testing if tumour biopsy was feasible. Patients who consented to prognostic testing received an explanation of their results from either a member of LOOC or a member of their clinical oncology team.

At diagnosis, all patients were asked if they were willing to participate in an audit to examine patient reported treatment outcomes. Patients who gave written consent were posted questionnaires at six observation points (6-, 12-, 24-, 36-, 48- and 60-months after diagnosis) with enclosed postage-paid envelopes. Surgical and radiographic treatments and communication of prognostic test results were completed before the initial 6-month observation. To examine long-term survivorship whilst minimising error in missing data estimation, patients were included if they contributed data at the 6-month observation and did not miss two consecutive observations after that point.

Measures

Demographic, clinical and treatment variables were collected from clinical records. These included age, gender, relationship and employment status, vision quality (visual acuity measured by logMar values converted from Snellen test scores[28] in the unaffected eye at diagnosis), tumour origin (choroid or ciliary body) and primary treatment type including whether the affected eye was conserved or removed (enucleation). Metastatic disease develops almost exclusively in patients whose tumour shows deletion of one of the normal two copies of chromosome 3 (monosomy 3 (M3); disomy 3 is normal maternal and paternal copies of chromosome 3).[22] For the present analysis, outcomes of testing were categorized as: M3 and disomy 3 and unknown (comprising patients who did not wish to be tested, where tumour characteristics did not suggest likely M3, and those whose genetic test failed).

Anxiety and depression symptoms were measured using the subscales of the Hospital Anxiety and Depression Scale (HADS),[29] which predicts anxiety and depression diagnoses.[30] Participants rate the extent to which they have experienced common symptoms of anxiety (7 items) and depression (7 items) in the preceding week using a 4-point Likert scale. Items are summed to give scores for anxiety and depression (range 0-21 for each); higher scores indicate greater anxious and depressive symptomatology, respectively.

Post-treatment symptoms and functional problems were measured using the European Organisation for Research and Treatment for Cancer Ophthalmic Quality of Life questionnaire

(EORTC OPT 30),[31] designed for UM patients and validated in UM samples.[32] Subscales or items pertaining only to subsamples, such as having received enucleation treatment or problems with driving, were not used. Subscales used in this study were: ocular irritation (e.g., discharge from the eye), a 6-item scale with Cronbach alphas in the current sample of .71 at 6 months and .75 at 12 months; vision impairment (e.g., troubled by any defects in side vision), a 4-item scale with alpha of .69 at 6-months and .73 at 12; a single item measuring headache ('Did you have headaches?'), functional problems (e.g., 'Difficulty seeing steps or pavements?'), difficulty reading and concerns about appearance. Response format for all EORTC OPT 30 items is 'Not at all', 'A little', 'Quite a bit' and 'Very much', scored 1-4, respectively. Higher scores indicate poorer outcomes. To simplify analysis, confirmatory factor analysis was used to test a single latent factor model consisting of the six subscales. A final single factor model showed satisfactory fit, $X^2_{(2.65)}$ =15.87, CFI=.98, RMSEA=.06. The six scales were reduced to a single mean of the six.

The EORTC OPT 30 has a 4-item scale for worry about recurrence (WREC). This study was designed before much of the FCR literature and its measures emerged. On the basis of item similarity with current FCR scales, we argue that the WREC scale appropriately assesses FCR. Three items were used, with an alpha of .87 at 6 months and .85 at 12 months: 'Were you worried about your health in the future?'; 'Were you worried about the tumour recurring in the treated eye?' and 'Were you worried about the tumour recurring in other areas of your body?' An item on concern about loss of the eye was excluded because it was irrelevant to enucleated patients. Response format for all EORTC OPT 30 items is 'Not at all', 'A little', 'Quite a bit' and 'Very much', scored 1-4, respectively. Higher scores indicate higher concerns.

Statistical Methods

Cross-lagged analyses were performed using structural equation modelling in Amos 24. Cross-lagged analyses examine prospective relationships between variables whilst controlling autocorrelation. Key events can be temporally located (for example, in a 6-, 12-, and 24-month observation design, prediction of a 24-month variable by a 12-month variable means that a 12-

to 24-month change in the outcome was caused by an earlier 6- to 12-month change in the predictor) but cause not fully proven.

Separate analyses were conducted for anxiety and depression. Cross-lagged predictor variables were concerns about physical symptoms and functional problems, WREC and anxiety or depression. Age, gender, treatment modality, visual acuity of the fellow eye, whether survivors were M3 or not (of which survivors are informed before the 6-month observation point) were initially used as covariates. Maximum likelihood estimation was made using unbiased covariances. Goodness of model fit was assessed by CMIN, CFI and RMSEA. Missing data were replaced using full information maximum likelihood estimation. Predictive paths were identified by noting sequences in significant cross-paths (e.g., a reciprocal path might be 6-month physical problems predicting 12-month anxiety, which then predicts 24-month physical problems).

Bias in retention was assessed using multivariate logistic regression to predict the 453 survivors who met inclusion criteria from characteristics of the 814 who provided data at 6-months. Predictors were age sex, treatment type (enucleation, plaque radiotherapy, proton beam radiotherapy, resection or other), M3, and 6-month physical symptoms, functional problems, WREC, depression and anxiety.

Results

Of 1,471 patients approached, 55.4% (814) completed the 6-month observation. Of these 814, 773 contributed at 12 months (95.0%), 706 at 24 (86.7%), 619 at 36 (76.1%), 557 at 48 (68.4%), and 438 at 60 (53.8%). The final sample was 453 patients (55.7% of 814), 240 males (53.0%) and 213 females (47.0%) with mean age at treatment of 69.48 (SD=11.57). Table 1 shows participant characteristics.

Table 2 shows means, SDs and temporal trends in study variables. Concerns mean item scores were midway between the item labels ‘not [concerning] at all’ and ‘a bit (concerning), WREC means of about 2.00 correspond to item label ‘quite a bit [concerning]’. Subscale means

were broadly similar to community norms. Anxiety and depression mean scores did not change over the five years, whilst concerns and WREC reduced. Correlations can be found in Appendix 1, and show positive associations, cross-sectionally and prospectively, between all variables.

Cross-Lagged Model for Anxiety

Treatment modality and visual acuity of the fellow eye did not improve models or predict any study variables. These were omitted from the reported model. Age, sex and M3 status were used as covariates. The full-sample model for anxiety did not show good fit (CMIN(*df*=6.47)=879.23, CFI=.890, RMSEA=.083).[33] A multigroup model based on gender showed better fit (CMIN(*df*=350)=1259.95, CFI=.885, RMSEA=.076), and significant differences in structural relationships between male and female analyses (CMIN=90.14 (df=51), p<.001). Figure 1 shows significant structural relationships for each gender (see appendices 2 and 3 for full structural relationships).

Younger survivors of both genders showed greater 6-month worry about recurrence and anxiety than older, and younger female survivors reported greater concerns. M3 survivors[1] of both genders showed greater worry, suggesting that survivors' 6-month worries were consistent with objective risk.

Direct Paths: Concerns at 6 months predicted anxiety at 12 months in males only. As a pre-treatment baseline was not used, it is not clear whether 6-month concerns that emerged before or after treatment. Worry at 24 months also predicted 36-month anxiety. In females, WREC at 12 months predicted anxiety at 24.

Indirect Paths: Males did not show indirect paths, but females showed two paths. Concerns at 6 months predicted 12-month worry, which then predicted anxiety at 24 months. 36-month concerns predicted 48-month worry, which predicted 60-month anxiety.

[1] We also assessed the effect of disomy 3 status on the model, finding, the opposite of M3 status, that disomy 3 predicted less anxiety and depression without influencing the significance of other components of the structural model.

Reciprocal Paths: A single reciprocal path was found. In males, 12-month anxiety predicted 24-month worry, which then predicted 36-month anxiety.

Cross-Lagged Model for Depression

The same covariates were used as the anxiety analysis. Again, better fit was obtained for a multigroup gender model ($CMIN_{(240)}$ =1065, CFI=.955, RMSEA=.077; full sample model $X^2_{(6.72)}$ =713.71, CFI=.88, RMSEA=.11) with significant structural differences between males and females (CMIN=93.62 (df=51) p<.001). Figure 2 shows structural relationships (see appendices 2 and 3 for full relationships). M3 survivors of both genders showed greater worry, and female M3 survivors showed higher depression scores at 12 months. Younger survivors of both genders showed higher 6-month worry and female younger survivors showed higher concerns and depression.

Direct Paths: For both genders, 24-month concerns predicted 36-month depression, and 36-month concerns predicted 48-month depression. In females, 24-month FCR predicted 36-month depression, and 36-month WREC predicted 48-month depression

Indirect Paths: There were no indirect paths.

Reciprocal Paths: In males, 12-month depression predicted 24-month concerns which predicted 36-month depression. In females, 24-month depression predicted 36-month concerns which predicted 48-month depression.

Retention Analysis

Binary logistic regression, using all 6-month variables as predictors, showed a multivariate difference between the 453 retained and non-retained participants in the 6-month observations (chi-sq=18.82, df=9, Nagelkerke R^2=.10, p<.05). Not being M3 positive predicted retention (odds ratio=1.92, lower 95% C.I.=1.24, upper 95% C.I.= 2.96). Half (112; 46.1%) of M3 positive survivors were retained. Ten died during the study. Three hundred and forty-one (59.7%) disomy 3 survivors were retained. Seven died during the course of the study.

Discussion

We found some evidence for our predicted paths. Concerns over physical symptoms and functional difficulties and worry *directly* predicted subsequent anxiety and depression. WREC mediated[2] an *indirect* path between concerns and anxiety and depression in females. In *reciprocal* paths, anxiety and depression predicted concerns, which in turn predicted anxiety and depression. Path initiation frequently post-dated completion of primary treatment, suggesting that symptoms, functional problems and worry arising during survivorship may cause anxiety and depression.

Findings extend cross-sectional[2,4,12,14] and prospective[17] evidence. Specific conclusions can now be drawn about time-frames within which effects occurred. In particular, we suggest that anxiety and depression are consequences of the dynamic process of how patients' concerns and worries develop and remit during survival, not mere consequences of diagnosis or treatment. Second, the temporal sequence of prediction provides the strongest support yet for a causal argument, although spurious effects from unmeasured variables are possible.

We did not investigate mechanisms underpinning paths, but we advance plausible hypotheses. Effects of symptoms, such as pain, and functional limitation on anxiety and depression, are well documented in the cancer and wider literature.[34,35] Perceived physical symptoms may increase the salience of survivors' negative memories and thoughts about their illnesses.[16] In particular, visual disturbances and physical sensations in and around the eye, measured by the EORTC OPT 30, could evoke traumatic memories of diagnosis or treatment. Research is needed to elucidate mediators and moderators of relationships between concerns about physical symptoms and functional problems and anxiety and depression.

Worry about recurrence, the scale we used to operationalise FRC, may mediate effects of concerns on anxiety.[17] As emphasised in several studies,[14, 16, 26] physical symptoms and functional problems cause FCR. We speculate that perceived physical symptoms, particularly

[2] Unmeasured variables may create spurious effects. Thus, true causal mediation cannot be proved. For brevity, the term 'mediation' is used, but this limitation should be borne in mind.

in and around the eye, might be either mistaken for cancer or cause worry by reminding survivors of cancer experiences.[15] M3 positive status predicted higher worry scores, suggesting that FCR is partly based in objective risk. However, changes in concerns predicted worry after M3 status was known, suggesting that indirect paths were largely independent of prognosis. Non-mediation of depression by worry may not be surprising in the light of a distinction between both worry and anxiety as deriving from future-oriented cognitions, associated with the prospect of loss or harm, such as cancer recurrence, whereas depression is rooted in experiences of past loss.[36]

Reciprocal paths suggest that anxiety and depression cause concerns about physical symptoms or functional problems, potentially worsening the initial anxiety or depression. This could enmesh survivors in a spiral of increasing anxiety and depression. There are two reasons that anxiety and depression might increase concerns or FCR. Anxiety and depression are risk factors for cancer symptom progression. This may be biologically mediated.[37] From a psychological perspective, negative interpretive biases associated with anxiety and depression could cause survivors to adversely interpret their existing symptoms and functional limitations.[20] If so, even sub-clinical levels of anxiety and depression might require intervention to prevent future deterioration.

Structural models differed for males and females. Paths were broadly similar across genders, but occurred at different observations. Indirect prediction of FCR was limited to females. Females had higher FCR scores, and it may be that worry about recurrence is more likely to be activated in females than males,[38] and consequently more likely to activate anxiety.

Study limitations

Generalisation to other cancers must be made carefully. We particularly note the relatively low concerns survivors expressed, and mean anxiety and depression scores that were not greater than those of age-matched healthy populations.[3] Cancers associated with higher concerns and HADS scores, might show differing structural relationships. The retention rate of 54% over five years is reasonable and we found little retention bias, but 55% of eligible patients

did not enter this study. Non-participants' characteristics may differ from participants',[23,24] and we do not know how non-participation affected findings. Effect sizes were small, but cross-lagged models provide conservative estimates when temporal stability is high.[39] We observed large stability coefficients, and structural coefficients that were typically smaller than their corresponding univariate correlations. Thus, effects may be larger than cross-lagged models suggest. Our objective was to examine predictors of symptomology in a large sample of UM survivors. We did not apply psychiatric inclusion or exclusion criteria. Thus, findings should not be interpreted in terms of predictors of diagnosed cases. Also, we did not collect data pertaining to psychological or pharmacological treatments. Where cases are successfully treated, this will probably lead to attenuation of relationships between predictor and outcome variables.

Clinical implications

Most paths originated during survivorship, but medical, social and psychological support for patients focusses on diagnosis and treatment, rather than survivorship.[40] A key study outcome is identifying risk factors for anxiety and depression through survivors' concerns about physical symptoms, functional problems and FCR. Reciprocal effects suggest that even sub-clinical anxiety or depression constitute potential risk factors.

One recommendation is to develop programmes that monitor survivors' anxiety, depression, concerns about physical symptoms and functional problems and FCR. Part of prevention will involve alleviating post-treatment medical problems, although many are not easily treated. Thus, education programmes are important to help survivors to anticipate and understand the implications of symptoms and functional problems, particularly in relation to FCR. Where perceptions of symptoms, functional limitations and recurrence risk are unrealistic, accurate information may help. Where these are objectively problematic, programmes based in coping, metacognitive, mindfulness and acceptance and commitment approaches might help survivors to meet challenges.[25]

Conclusions

New interventions will need to be underpinned by research that develops better understandings of why survivors' concerns about symptoms and functional problems render them directly vulnerable to worry about anxiety and depression, and indirectly vulnerable through FCR.

Conflict of Interest: The authors have no conflicts of interest to declare.

Data Availability: Data available on request from the first author. Ethical clearance may be required before data can be provided.

Acknowledgements: We thank Nicola Longrigg and Gary Cheetham for their expertise and assistance with data management.

References

1. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. *BMJ.* 2005; 330(702). https://doi.org/10.1136/bmj.38343.670868.d3

2. Hoffman KE, McCarthy EP, Recklitis CJ, Ng AK. Psychological distress in long-term survivors of adult-onset cancer: results from a national survey. *Arch Int Med* 2009; 169:1274-1281. https://doi.org/10.1001/archinternmed.2009.179

3. Hope-Stone L, Brown SL, Heimann H, Damato B, Salmon P. Two-year patient-reported outcomes following treatment for uveal melanoma. *Eye* 2016; 30:1598-1605. https://doi.org/10.1038/eye.2016.188

4. Sharpley C, Christie D, Bitsika V. Variability in anxiety and depression over time following diagnosis in patients with prostate cancer. *J Psychosoc Oncol.* 2010;28:644-652. https://doi.org/10.1080/07347332.2010.516810

5. Philip E, Merluzzi T, Zhang Z, Heitzmann C. Depression and cancer survivorship: importance of coping self-efficacy in post-treatment survivors. *Psycho-oncol* 2013; 22:987-994. https://doi.org/10.1002/pon.3088

6. Colleoni M, Mandala M, Peruzzotti G, Robertson C, Bredart A, Goldhirsch A. Depression and degree of acceptance of adjuvant cytotoxic drugs. *Lancet* 2000; 356:1326-1327. https://doi.org/10.1016/s0140-6736(00)02821-x

7. Manning M, Bettencourt B. Depression and medication adherence among breast cancer survivors: bridging the gap with the theory of planned behaviour. *Psychol Health* 2011; 26:1173-1187.https://doi.org/10.1080/08870446.2010.542815

8. Fiszer C, Dolbeault S, Sultan S, Bredart A. Prevalence, intensity, and predictors of the supportive care needs of women diagnosed with breast cancer: a systematic review. *Psycho-oncology* 2014; 23:361-374. https://doi.org/10.1002/pon.3432

9. Cook S, Salmon P, Hayes G, Byrne A, Fisher P. Predictors of emotional distress a year or more after diagnosis of cancer: A systematic review of the literature. *Psycho-oncol* 2018; 27:791- 801; https://doi.org/10.1002/pon.4601

10. Phillips AC, Carroll D, Der G. Negative life events and symptoms of depression and anxiety: stress causation and/or stress generation. *Anxiety Stress Coping* 2015; 28:357-371. https://doi.org/10.1080/10615806.2015.1005078

11. Elliott J, Fallows A, Staetsky L, et al. The health and well-being of cancer survivors in the UK: findings from a population-based survey. *Brit J Cancer* 2011; 105:S11-S20. https://doi.org/10.1038/bjc.2011.418

12. Deimling G, Bowman K, Sterns S, Wagner L, Kahana B. Cancer-related health worries and psychological distress among older adult, long-term cancer survivors. *Psycho-oncol* 2006; 15:306-320. https://doi.org/10.1002/pon.955

13. Dempsey LE, Karver MS, Labouliere C, Zesiewicz TA, De Nadai AS. Self-perceived burden as a mediator of depression symptoms amongst individuals living with a movement disorder. *J Clin Psychol* 2012; 68:1149-1160. https://doi.org/10.1002/jclp.21901

14. Simonelli L, Siegel S, Duffy N. Fear of cancer recurrence: a theoretical review and its relevance for clinical presentation and management. *Psycho-oncol* 2016; 26:1444-1454. https://doi.org/10.1002/pon.4168

15. Fardell J, Thewes B, Turner J, et al. Fear of cancer recurrence: a theoretical review and novel cognitive processing formulation. *J Cancer Survivorship* 2016; 10:663-673. https://doi.org/10.1007/s11764-015-0512-5

16. Freeman-Gibb L, Janz N, Katapodi M, Zikmund-Fisher B, Northouse L. The relationship between illness representations, risk perception and fear of cancer recurrence in breast cancer survivors. *Psycho-oncol* 2017; 26:1270-1277. https://doi.org/10.1002/pon.4143

17. Brown S, Hope-Stone L, Heimann H, Damato B, Salmon P. Predictors of anxiety and depression 2 years following treatment in uveal melanoma survivors. *Psycho-oncol* 2018; 27:1727-1734. https://doi.org/10.1002/pon.4715

18. Mohammadpour H, Bucsek MJ, Hylander BL, Repasky EA. Depression stresses the immune response and promotes prostate cancer growth. *Clin Cancer Res* 2019; 25:2363-2365. https://doi.org/10.1158/1078-0432.ccr-18-3980

19. Markovitz L, Drysdale N, Bettencourt B. The relationship between risk factors and medication adherence among breast cancer survivors: What explanatory role might depression play? *Psycho-oncol* 2017; 26:2294-2299. https://doi.org/10.1002/pon.4362

20. Lam WWT, Ng D, Wong S, Lee TMC, Kwong A, Fielding R. The role of cognitive bias in relation to persistent distress among women diagnosed with breast cancer. *Psycho-oncol* 2018; 27:983-989. https://doi.org/10.1002/pon.4620

21. Kaliki S, Sheilds C. Uveal Melanoma: relatively rare but deadly cancer. *Eye* 2017; 31:241-257. https://doi.org/10.1038/eye.2016.275

22. Damato B. Does ocular treatment of uveal melanoma influence survival? *Brit J Cancer* 2010; 103:285-290. https://doi.org/10.1038/sj.bjc.6605765

23. Damato B, Hope-Stone L, Cooper B, Brown S, Heimann H, Dunn L. Patient-reported outcomes and quality of life after treatment for choroidal melanoma. *Ocular Oncol Path* 2019 ;5:402-411. https://doi.org/10.1159/000496927

24. Damato B, Hope-Stone L, Cooper B, Salmon P, Heimann H, Dunn L. Patient-reported outcomes and quality of life after treatment of choroidal melamona: a comparison of enucleation versus radiotherapy in 1596 patients. *Am J Opthalmol* 2018; 193:230-251. https://doi.org/10.1016/j.ajo.2018.03.015

25. Cherry M, Salmon P, Byrne A, Ullmer H, Abbey G, Fisher P. Qualitative evaluation of cancer survivors' experiences of metacognitive therapy: a new perspective on psychotherapy in cancer care. *Frontiers Psychol* 2019; 10. https://doi.org/10.3389/fpsyg.2019.00949

26. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari, S, Ozakinci G. Fear of cancer recurrence in adult cancer survivors: a systematic review. *J Cancer Survivorship* 2013; 7:300-322. https://doi.org/10.1007/s11764-013-0272-z

27. Damato B, Heimann H. Personalized treatment of uveal melanoma. *Eye* 2013; 27:172-179. https://doi.org/10.1038/eye.2012.242

28. Holladay J. Visual acuity measurements. *J Cataract Refractary Surg.* 2004; 30:287-290. https://doi.org/10.1016/j.jcrs.2004.01.014

29. Zigmond A, Snaith R. The Hospital Anxiety and Depression Scale. *Acta Psychiat Scand.* 1983; 67:361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

30. Vodermaier A, Millman RD. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: a systematic review and meta-analysis. *Supportive Care Cancer.* 2011; 19:1899-1908. https://doi.org/10.1007/s00520-011-1251-4

31. Brandberg Y, Damato B, Kivela T, Kock E, Seregard S. The EORTC Opthalmic Oncology Quality of Life Questionnaire Module (EORTC QLQ-OPT30) Development and pre-testing. *Eye* 2004; 14:839-846. https://doi.org/10.1038/sj.eye.6700639

32. Chmielowska K, Tomaszewski K, Pogrzebielski A, Brandberg Y, Romanowska-Dixon B. Translation and validation of the Polish version of the EORTC QLQ-OPT30 module for the assessment of health-related quality of life in patients with uveal melanoma. *Euro J Cancer Care.* 2013; 22:88-96. https://doi.org/10.1111/ecc.12001

33. Marsh HW, Hau KT, Wen Z. In search of golden rules: Comment on hypothesis-testing approaches to setting cutoff values for fit indexes and dangers in overgeneralizing Hu and Bentler's (1999) findings. *Struct Equation Modeling.* 2004; 11;320-341. https://doi.org/10.1207/s15328007sem1103_2

34. Burke A, Mathias J, Denson L. Psychological functioning of people living with chronic pain: a meta-analytic review. *Brit J Clin Psychol* 2015; 54:345-360. https://doi.org/10.1111/bjc.12078

35. Laird B, Boyd A, Colvin L, Fallon M. Are cancer pain and depression interdependent? A systematic review. *Psycho-Oncol* 2009; 18:459-464. https://doi.org/10.1002/pon.1431

36. Eysenck M, Payne S, Santos R. Anxiety and depression: Past, present, and future events. *Cognition Emot* 2006; 20:274-294. https://doi.org/10.1080/02699930500220066

37. Batty G, Russ T, MacBeath M, Stamatakis E, Kivimäki M. Psychological distress in relation to site specific cancer mortality: pooling of unpublished data from 16 prospective cohort studies. *BMJ* 2017;356. https://doi.org/10.1136/bmj.j108

38. Götze H, Taubenheim S, Dietz A, Lordick F, Mehnert-Theuerkauf A. Fear of cancer recurrence across the survivorship trajectory: Results from a survey of adult long-term cancer survivors. *Psycho-Oncol* 2019; 28:233-241. https://doi.org/10.1002/pon.5188

39. Adachi P, Willoughby T. Interpreting effect sizes when controlling for stability effects in autoregressive models: Implications for psychological science. *Euro J Developmental Psychol* 2014; 12:116-128. https://doi.org/10.1080/17405629.2014.963549

40. Brennan J. *Cancer in Context: A Practical Guide to Supportive Care.* Oxford: OUP; 2004. https://doi.org/10.1002/pon.1027

Table 1: Participant Characteristics

Table 2: Means and Standard Deviations of Study Measures and Analysis of Temporal Trends

Figure 1: Cross-Lagged Analysis Showing Significant Structural Relationships Between Predictors and Anxiety for Males (M) and Females (F). Bold Arrows Indicate Significant Paths for One or Both Genders. Full Structural Coefficients for Both Genders are in Appendix 2.

Figure 2: Cross-Lagged Analysis Showing Significant Structural Relationships Between Predictors and Depression for Males (M) and Females (F). Bold Arrows Indicate Significant Paths for One or Both Genders. Full Structural Coefficients for Both Genders are in Appendix 2.

Table 1: Participant Characteristics

	Value	Mean or Frequency	*SD* or Percentage
Relationship Status	Relationship	348	76.8%
	Divorce/Separate	27	6.0%
	Widowed	48	10.6%
	Single	29	6.4%
Employment Status	Employed	171	37.7%
	Homemaker	16	3.5%
	Retired	221	48.8%
	Unemployed	8	1.8%
	Sickness leave	17	3.8%
	Student	14	3.1%
	Unknown	6	1.3%
Affected Eye	Left	222	49.0%
	Right	231	51.0%
Visual acuity* (Affected eye)		1.22	0.27
Visual acuity (Unffected eye)		1.43	0.28
Chromosome 3 Status	Monosomy 3	118	26.0%
	Disomy 3	135	29.8%
	Did not accept test	164	36.2%
	Biopsy failed	36	8.0%
Treatment	Plaque radiotherapy	219	48.3%
	Proton beam radiotherapy	99	21.9%
	Enucleation	92	20.3%
	Resection	26	5.7%
	Other	17	3.8%

* Visual acuity is presented in the logmar scale (converted from Snellen scores). Scores of zero indicating good vision, negative values better vision and positive values worse vision.

** This includes patients who were not offered tests, who refused tests or testing failed.

Note: *SD* = standard deviation

Table 2: Means and Standard Deviations of Study Measures and Analysis of Temporal Trends

	Anxiety		**Depression**		**Concerns**		**Worry About Recurrence**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
6 months	5.12	4.01	2.93	3.09	1.53	0.43	2.34	0.88
12 months	4.83	4.03	2.99	3.21	1.51	0.43	2.10	0.79
24 months	4.86	3.86	2.90	3.15	1.49	0.43	2.04	0.75
36 months	4.90	4.09	3.09	3.51	1.49	0.42	1.95	0.74
48 months	4.86	4.07	3.19	3.27	1.46	0.41	1.98	0.75
60 months	4.93	3.99	3.18	3.56	1.49	0.42	1.98	0.76
Trend	$F(5,1390)=1.01$, $p=.357$		$F(5,1390)=2.04$, $p=.070$		$F(5,1390)=2.81$, $p<.05$		$F(5,1390)=27.31$, $p<.01$	

Note: SD = standard deviation

Figure 1: Cross-Lagged Analysis Showing Significant Structural Relationships Between Predictors and Anxiety for Males (M) and Females (F). Bold Arrows Indicate Significant Paths for One or Both Genders. Full Structural Coefficients for Both Genders are in Appendix 2. (WREC is worry about recurrence).

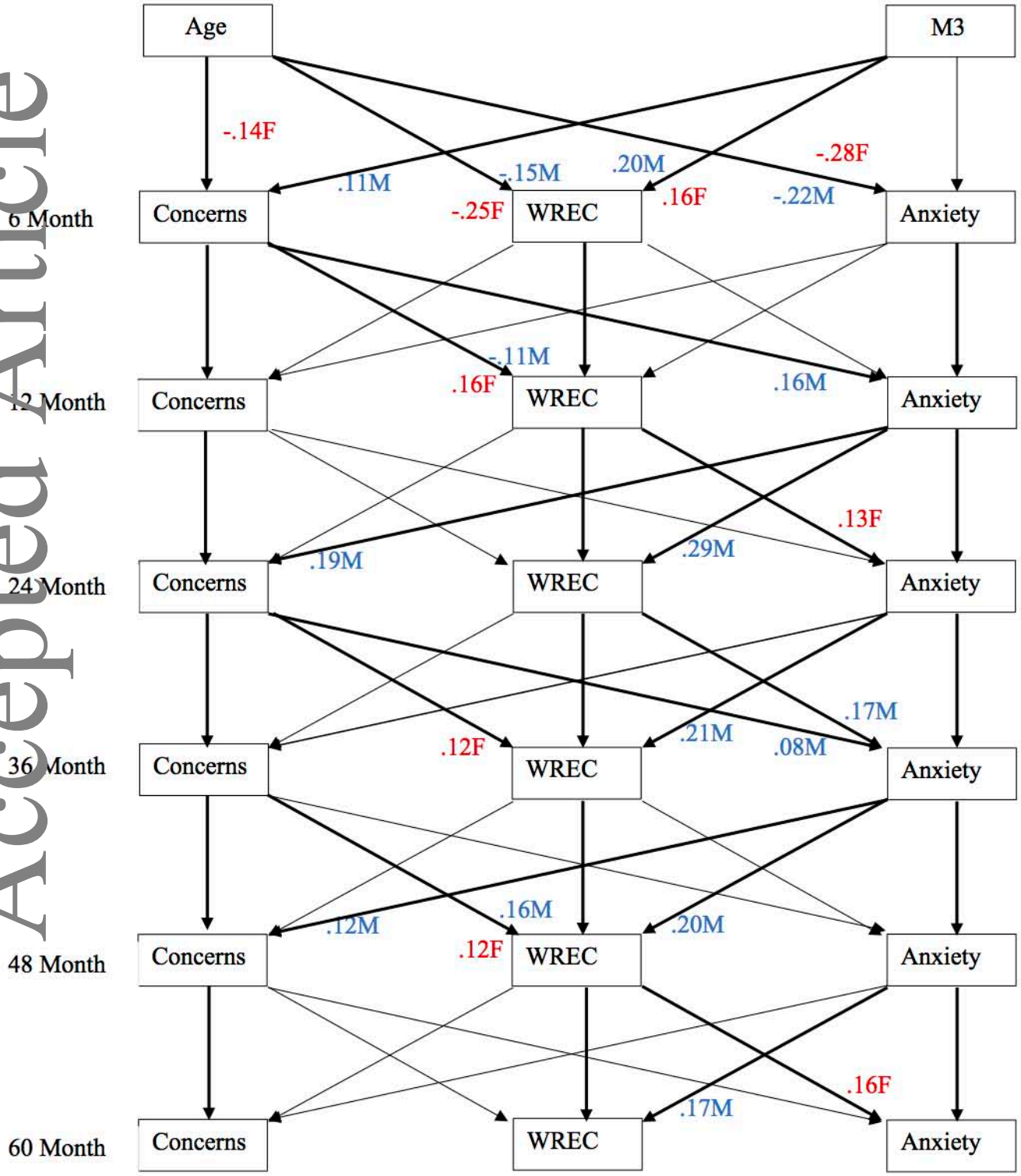

Figure 2: Cross-Lagged Analysis Showing Structural Relationships Between Predictors and Depression in Males (M) and Females (F). Bold Arrows Indicate Significant Paths for One or Both Genders. Full Structural Coefficients for Both Genders are in Appendix 2. (WREC is worry about recurrence).